Synthesis of Multilayered [3.3](3,5)Pyridinophanes

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Abstract: Two- to four-layered [3.3](3,5)pyridinophanes (PyPs) have been synthesized by the (4-tolylsulfonyl)methyl isocyanide (TosMIC) method. The coupling reaction between 3,5-bis[2-isocyano-2-(4-tolylsulfonyl)ethyl]pyridine (TosMIC adduct) and bis(chloromethyl) or tetrakis(bromomethyl) compounds in the presence of sodium hydride in N,N-dimethylformamide or sodium hydroxide and tetrabutylammonium iodide under high-dilution conditions gave the two-layered dione or three- and four-layered tetraones. Wolff–Kishner reduction of the ketones afforded the desired two- to four-layered [3.3](3,5)PyPs. The structure of the dione units take an anti geometry whereas the cyclophane units take a syn geometry in solution.

Key words: cyclophanes, pyridines, coupling reaction, ketones, Wolff–Kishner reduction

[3.3]Metapyridinophanes (MPyPs) are composed of two pyridine rings and two three-atom bridges connected to them. Among the various types of [3.3]MPyPs, the [3.3][2,6]PyPs have been studied in detail and the 2,11-diaza[3.3]MPyPs incorporate pyridine rings at both ends may form larger supramolecules upon complexation with the transition metals and new types of supramolecules may serve as catalysts, inclusion hosts, and nanometer-scale materials. We now report the synthesis of two- to four-layered [3.3](3,5)PyPs 1–3 and their structures in solution by 1H NMR studies.

Multilayered [3.3](3,5)PyPs 1–3 were synthesized by the TosMIC method in the critical coupling reaction (Scheme 1). The synthetic key intermediates for the synthesis of multilayered PyPs are bis(chloromethyl)pyridine 49 and its TosMIC adduct 6. 3,5-Bis(chloromethyl)pyridine (49) was synthesized by chlorination of 3,5-lutidine with N-chlorosuccinimide in carbon tetrachloride followed by column chromatography on silica gel (n-hexane–EtOAc, 3:1; Rf = 0.20) to give 49 in 32% yield. The chloride 49 was immediately reacted with (4-tolylsulfonyl)methyl isocyanide (TosMIC, 5) under phase-transfer conditions, and the crude product was purified by column chromatography on silica gel (EtOAc–n-hexane, 3:2; Rf = 0.34) to give the TosMIC adduct 6 in 14% yield. The reason for the relatively low yield of the TosMIC adduct 6 may be ascribed to the instability of the chloride 49. 3,5-Bis(chloromethyl)pyridine (49) was coupled with the TosMIC adduct 6 in the presence of sodium hydride in N,N-dimethylformamide at room temperature for 24 hours under nitrogen, followed by hydrolysis of the cyclic adduct with concentrated hydrochloric acid to give the two-layered dione 7 in 35% yield. Wolff–Kishner reduction of 7 and purification by column chromatography on silica gel (CH2Cl2–EtOH, 9:1; Rf = 0.46) afforded the two-layered PyP 1 in 93% yield. Thus, the parent [3.3](3,5)PyP has been synthesized for the first time, and successful isolation of the TosMIC adduct 6 was a key step in the synthesis of the multilayered [3.3](3,5)PyPs.

Tetrakis(bromomethyl) compounds 8 and 10 are versatile synthetic intermediates for the one-pot synthesis of three- and four-layered [3.3]MCPs, respectively. 12 1,2,4,5-Tetrakis(bromomethyl)benzene (8) was coupled with the
TosMIC adduct 6 in the presence of sodium hydroxide and tetrabutylammonium iodide in a mixture of dichloromethane and water under phase-transfer conditions at reflux, followed by hydrolysis with concentrated hydrochloric acid to provide the desired three-layered tetraone 9 in 4.5% yield. The Wolff–Kishner reduction of the tetraketone 9 gave the three-layered [3.3](3,5)PyP 2 in 75% yield after purification by column chromatography (silica gel, CH₂Cl₂–EtOH, 9:1; Rᵣ = 0.46). A similar coupling reaction of 5,7,14,16-tetrakis(bromomethyl)[3.3]MCP 10 prepared by the one-step bromomethylation of [3.3]MCP with the TosMIC adduct 6 afforded the four-layered tetraone 11, which was converted into the four-layered [3.3](3,5)PyP 3 by Wolff–Kishner reduction in 81% yield after purification by column chromatography (silica gel, CH₂Cl₂–EtOH, 9:1; Rᵣ = 0.53).

It is known that [3.3]MCP and its dione adopt different syn and anti geometry as stable conformers in solution, respectively, and we have studied the conformational behavior of the [3.3]MCPs and related systems in detail. Moreover, we have recently reported the structural properties of the multilayered [3.3]MCPs in solution and in the solid state, in which the [3.3]MCP moiety takes the syn geometry whereas the [3.3]MCP-dione moiety takes the anti geometry. This indicated that the original stable conformations are maintained even in the multilayered [3.3]MCPs. Similarly, the [3.3]MCP units assume syn geometry in multilayered [3.3](3,5)PyPs 1–3 (Figure 2). The Hᵢ₁ protons of the two-layered 1 appear at the normal position, which is comparable to that of [3.3]MCP, while the inner aromatic protons, Hᵢ₃ in the three-layered 2 and Hᵢ₃ and Hᵢ₅ in the four-layered 3, are moderately shielded due to the diamagnetic ring current effect of the stacked aromatic rings. This indicates the syn-syn and syn-syn-syn geometries for 2 and 3, respectively. All the aromatic protons of 2 and 3 are assigned on the basis of their NOESY spectra, in which the correlations are observed between Hᵢ₁–Hᵢ₃, Hᵢ₂–Hᵢ₅, and Hᵢ₅–Hᵢ₇ in the three-layered 2 (Figure 3). As for the four-layered 3, the correlations are

\[ \text{Scheme 1} \quad \text{Synthetic route to two- to four-layered [3.3](3,5)pyridinophanes 1–3} \]
Figure 2  Selected 1H NMR data of the aromatic protons of multilayered [3.3](3,5)PyPs and diones (δ, 300 MHz, CDCl3)

observed between Hi1–Hi3, Ha–Hb, and Ha–Hc, while the correlation between Hi1–Hi4 is not observed (Figure 4). These results suggest the all-syn geometries for 2 and 3. In contrast, multilayered [3.3](3,5)PyPs with dione units take an anti geometry as shown in Hi2 in the two-layered 7, Hi1 in the three-layered 9, and Hi1 and Hi2 in the four-layered 11 due to the ring current effect of the faced aromatic rings, and this suggests anti, anti-anti, and anti-syn-anti geometries for 7, 9, and 11, respectively. Thus multilayered [3.3]PyPs take structures similar to the corresponding multilayered [3.3]MCPs in solution.

In conclusion, we have synthesized the TosMIC adduct of 3,5-bis(chloromethyl)pyridine 6, and the coupling of 6 with the bis- or tetrakis(halomethyl) compounds 4, 8, and 10 in the presence of sodium hydride in N,N-dimethylformamide or sodium hydroxide and tetrabutylammonium iodide in a mixture of dichloromethane and water under phase-transfer conditions gave the two- to four-layered [3.3](3,5)PyPs 1–3, respectively. Similar to the structure of the multilayered [3.3]MCPs in solution, multilayered [3.3](3,5)PyPs 1–3 take the all-syn conformation, while the [3.3](3,5)PyP-dione moieties in 7, 9, and 11 assume anti geometry. Currently, we are investigating their structures in the solid state, complexity behavior, and conformational analysis, and these results will be reported elsewhere.

All melting points were measured on a Stuart Scientific Melting Point Apparatus SMP3, and are uncorrected. The 1H and 13C NMR spectra were measured using Jeol JNM-AL300, Jeol JNM-ECA600, and Bruker ARX-300 spectrometers; internal reference was TMS and the solvent was CDCl3 or CD2Cl2 unless otherwise noted. The MS (FAB-MS, m-nitrobenzyl alcohol) were obtained using a Jeol JMS-SX/SX 102A mass spectrometer. The IR spectra were measured with a Nicolet Impact 400D spectrophotometer. The elemental analyses were performed by the Service Centre of the Elementary Analysis of Organic Compounds affiliated with the Faculty of Science, Kyushu University.

The analytical TLC was performed on Silica gel 60 F254 Merck. Column chromatography was performed on Kanto silica gel 60N (63–210 μm). All solvents and reagents were of reagent quality, commercially purchased, and used without further purification, except as noted. 3,5-Bis(chloromethyl)pyridine6 and TosMIC (except for the use of dioxane in place of DME)15 were prepared according to the literature procedures.

3,5-Bis[2-isocyano-2-(4-tolylsulfonyl)ethyl]pyridine (6)

A mixture of n-Bu4NI (0.73 g), CH2Cl2 (50 mL), and NaOH (8 g) dissolved in H2O (32 mL) was stirred in an ice bath. To the mixture was added in one portion to a soln of TosMIC (5, 7.3 g, 37.5 mmol) in CH2Cl2 (40 mL). After 30 min, to the mixture in an ice bath was added freshly prepared chloride 4 (1.80 g, 10.2 mmol) in CH2Cl2 (50 mL) in one portion and the mixture was stirred for ca. 10 h in the ice bath. The mixture was then allowed to warm up to r.t. overnight. The mixture was washed with H2O, dried (MgSO4), filtered, and concentrated to a volume of ca. 30 mL at 25 °C. The concentrate was purified by column chromatography (silica gel, CH2Cl2 then EtOAc–hexane, 3:2; Rf = 0.34). The eluate was concentrated to a volume of ca. 30 mL, then CCl4 was added (100 mL). The soln was concentrated to a volume of ca. 30 mL at 35 °C. The precipitate was collected by filtration and suspended in a small amount of cold acetone. The insoluble solid was collected by filtration to give the TosMIC adduct 6 (721 mg, 14%) as a white powder; mp 105 °C (dec).

IR (KBr): 2136, 1333, 1151 cm−1.

1H NMR (300 MHz, CDCl3): δ = 2.50 (s, 6 H, CH3), 3.07 (dd, J = 14.0, 11.2 Hz, 2 H, CH2CH), 3.61 (dd, J = 14.1, 3.2 Hz, 2 H, CH2CH), 4.58 (dd, J = 11.1, 3.3 Hz, 2 H, CH2CH), 7.46 (d, J = 8.0 Hz, 4 H, TsH), 7.56 (t, J = 2.1 Hz, 1 H, PyH), 7.90 (dd, J = 6.7, 1.6 Hz, 4 H, TsH), 8.53 (d, J = 2.1 Hz, 2 H, PyH).

13C NMR (150 MHz, CDCl3): δ = 22.0, 32.3, 73.6, 129.9, 130.4, 130.8, 131.3, 138.2, 147.8, 150.6, 167.1.


Two-Layered [3.3](3,5)Pyridophane (1)

To a mixture of NaH (60%, 0.25 g, 10.4 mmol) and DMF (80 mL) was dropped in a mixture of chloride 4 (317 mg, 1.80 mmol) and TosMIC adduct 6 (887 mg, 1.80 mmol) dissolved in DMF (200 mL) at r.t. over a period of 7 h and the mixture was stirred at r.t. for an additional 16 h. The solvent was removed under reduced pressure and MeOH was added to the residue and the insoluble solid was washed with H2O, then the insoluble solid was further washed with CH2Cl2, and then CH2Cl2 was added to the residue. The precipitate was collected by filtration to give 1 (721 mg, 14%) as a white powder; mp 220–221 °C (dec).

IR (KBr): 3400, 2920, 1780, 1720, 1630, 1580, 1510, 1460, 1380, 1280, 1120, 850 cm−1.


collected by filtration to give the cyclic TosMIC adduct as a pale brown powder.

To a mixture of the cyclic TosMIC adduct and CH$_2$Cl$_2$ (150 mL) was added concd HCl (5 mL) and it was stirred at r.t. After 3 h, KOH (10 g) dissolved in H$_2$O (30 mL) was added and the mixture was stirred at r.t. for 1 h. The mixture was extracted with CH$_2$Cl$_2$. The CH$_2$Cl$_2$ soln was washed with H$_2$O, dried (MgSO$_4$), and concentrated to dryness. The resulting residue was washed with acetone to give the dione 7 (169 mg, 35% for two steps) as colorless needles (CHCl$_3$); mp 212 °C (dec).

IR (KBr): 1698 cm$^{-1}$.

$^1$H NMR (300 MHz, CDCl$_3$): $\delta$ = 3.62 (s, 8 H, C$_2$H$_2$COCH$_2$), 6.07 (t, $J$ = 2.1 Hz, 2 H, ArH), 8.51 (d, $J$ = 2.1 Hz, 4 H, ArH).

$^{13}$C NMR (75 MHz, CDCl$_3$): $\delta$ = 47.5, 129.0, 142.6, 149.8, 203.4.

HRMS (FAB): m/z [M + H]$^+$ calcd for C$_{16}$H$_{15}$N$_2$O$_2$: 267.1134; found: 267.1131.

Anal. Calcd for C$_{16}$H$_{14}$N$_2$O$_2$: C, 72.16; H, 5.30; N, 10.52. Found: C, 72.09; H, 5.32; N, 10.48.

A mixture of the dione 7 (169 mg, 35% for two steps) as colorless needles (CHCl$_3$); mp 212 °C (dec).

$^1$H NMR (300 MHz, CDCl$_3$): $\delta$ = 2.0–2.2 (m, 4 H, CH$_2$CH$_2$CH$_2$), 2.76 (t, $J$ = 5.8 Hz, 8 H, CH$_2$CH$_2$CH$_2$), 7.13 (t, $J$ = 1.9 Hz, 2 H, ArH), 7.90 (d, $J$ = 1.9 Hz, 4 H, ArH).

$^{13}$C NMR (75 MHz, CDCl$_3$): $\delta$ = 47.5, 129.0, 142.6, 149.8, 203.4.

HRMS (FAB): m/z [M + H]$^+$ calcd for C$_{16}$H$_{19}$N$_2$: 239.1548; found: 239.1549.

Anal. Calcd for C$_{16}$H$_{18}$N$_2$: C, 80.63; H, 7.61; N, 11.75. Found: C, 80.38; H, 7.57; N, 11.77.

Three-Layered [3.3](3,5)Pyridinophane (2)

A mixture of n-Bu$_4$NI (1.50 g), NaOH (25 g) dissolved in H$_2$O (75 mL) and CH$_2$Cl$_2$ (800 mL) was heated to reflux with stirring. To the mixture was dropwise added a mixture of tetrabromide 8 (758 mg, 1.69 mmol) and TosMIC adduct 6 (1.67 g, 3.38 mmol) in CH$_2$Cl$_2$ over a period of 11 h, and the mixture was refluxed for an additional 11 h. The cooled mixture was washed with H$_2$O and concentrated to a volume of ca. 200 mL.

To the concentrate was added concd HCl (50 mL) and the mixture was stirred at r.t. After 3.5 h, 3 M HCl (200 mL) was added in one portion and the mixture was stirred at r.t. for 1.5 h. The aqueous soln was basified by the addition of NaOH and the precipitate was filtered. The crude product was suspended in CHCl$_3$ (200 mL) at reflux and filtered. The filtrate was concentrated to dryness, suspended in a small amount of acetone and pyridine and sonicated. The insoluble solid was recrystallized (CHCl$_3$) to give the tetraone 9 (34.3 mg, 4.5%) as an ivory powder (CHCl$_3$); mp 241 °C (dec).

IR (KBr): 1701 cm$^{-1}$.
Synthesis of Multilayered [3.3](3,5)Pyridinophanes

**Figure 4** NOESY spectrum of four-layered [3.3](3,5)pyridinophane 3

1H NMR (300 MHz, CDCl₃): δ = 3.66 (s, 8 H, CH₂COCH₂), 3.69 (s, 8 H, CH₂COCH₂), 5.58 (s, 2 H, Hi₂), 6.69 (d, J = 2.1 Hz, 2 H, Hi₁), 8.50 (d, J = 2.1 Hz, 4 H, Ha).


A mixture of the tetracene 9 (65.8 mg, 0.145 mmol), KOH (2 g), 98% NH₂NH₂·H₂O (5 mL), and diethylene glycol (25 mL) was heated at 130 °C for 12 h and then at 200 °C for 4 h with stirring. After cooling, the mixture was poured into ice water and extracted with CH₂Cl₂. The CH₂Cl₂ soln was washed with brine, dried (MgSO₄), and concentrated to dryness. Purification of the residue by column chromatography (silica gel, CH₂Cl₂–EtOH, 9:1; Rf = 0.46) produced the three-layered pyridinophane 2 (43.3 mg, 75%) as a white powder (CH₂Cl₂–acetone); mp 285 °C (dec).

1H NMR (600 MHz, CDCl₃): δ = 1.9–2.1 (m, 8 H, CH₂C₆H₄CH₂), 2.5–2.7 (m, 16 H, C₆H₄CH₂C₆H₄), 6.17 (s, 2 H, Hi₂), 7.08 (s, 2 H, Hi₁), 7.78 (s, 4 H, Ha).

HRMS (FAB): m/z [M + H]+ calcd for C₂₈H₃₃N₂: 397.2644; found: 397.2640.

**Four-Layered [3.3](3,5)Pyridinophane (3)**

A mixture of n-Bu₄NI (0.75 g), NaOH (10 g) dissolved in H₂O (50 mL) and CH₂Cl₂ (450 mL) was heated to reflux with stirring. To the mixture was dropwise added a mixture of tetrabromide 10 (489 mg, 0.804 mmol) and TosMIC adduct 6 (800 mg, 1.62 mmol) in CH₂Cl₂ over a period of 7 h, and the mixture was refluxed for an additional 12 h. The cooled mixture was washed with H₂O and concentrated to a volume of ca. 200 mL.

To the concentrate was added conc HCl (15 mL) and the mixture was stirred at r.t. After 4 h, KOH (20 g) dissolved in H₂O (80 mL) was added in one portion and the mixture was stirred for 4.5 h at r.t. The mixture was then extracted with CH₂Cl₂. The CH₂Cl₂ soln was washed with H₂O, dried (MgSO₄), and concentrated to dryness. The residue was suspended in acetone and collected by filtration to give the crude ketone, which was suspended in pyridine and the insoluble solid was recrystallized (CHCl₃) to give the pure tetraone 11 (68 mg, 15%) as colorless needles (CHCl₃); mp 250 °C (dec).

IR (KBr): 1702 cm⁻¹.

1H NMR (300 MHz, CDCl₃): δ = 1.9–2.1 (m, 8 H, CH₂C₆H₄CH₂), 2.81 (t, J = 5.5 Hz, 8 H, CH₂C₆H₄CH₂), 3.36 (s, 16 H, C₆H₄COC₆H₄), 5.32 (s, 2 H, Hi₂), 5.72 (t, J = 2.0 Hz, 2 H, Hi₁), 7.01 (s, 2 H, Hi₁), 8.29 (d, J = 2.0 Hz, 4 H, Ha).

HRMS (FAB): m/z [M + H]+ calcd for C₄₀H₃₉N₂O₄: 611.2910; found: 611.2924.

A mixture of the tetraone 11 (142 mg, 0.233 mmol), 98% NH₂NH₂·H₂O (8 mL), and diethylene glycol (25 mL) was heated at 130 °C with stirring. After 20 h, KOH (2 g) was added and heated at 200 °C for 6 h with stirring. After cooling, the mixture was poured into ice water and extracted with CH₂Cl₂. The CH₂Cl₂ soln was washed with brine, dried (MgSO₄), and concentrated to dryness. Purification of the residue by column chromatography (silica
gel, CH₂Cl₂–EtOH, 9:1; Rₜ = 0.53) produced the four-layered pyri
dinophane 3 (105 mg, 81%) as colorless prisms (CH₂Cl₂–acetone); 
mp 245 °C (dec).

¹H NMR (600 MHz, CDCl₃): δ = 1.8–2.0 (m, 12 H, CH₂CH₂CH₂), 
2.4–2.7 (m, 24 H, CH₂CH₂CH₂), 5.97 (s, 2 H, H₆), 6.21 (s, 2 H, 
H₇), 6.91 (s, 2 H, H₈), 7.84 (d, J = 1.5 Hz, 4 H, Ha).

¹³C NMR (150 MHz, CDCl₃): δ = 26.2, 27.7, 32.4, 32.7, 33.2, 
130.4, 134.4, 134.8, 135.8, 140.4, 146.8.

HRMS (FAB): m/z [M + H]+ calcd for C₄₀H₄₇N₂: 555.3739; found: 
555.3739.

Anal. Calcd for C₄₀H₄₇N₂: C, 86.59; H, 8.36; N, 5.05. Found: C, 
86.35; H, 8.34; N, 5.01.

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